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Long Non-coding RNA in Liver Metabolism and Disease: Current Status

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Abstract

Long non-coding RNAs (lncRNAs) are comprised of RNA transcripts exceeding 200 nucleotides in length but lacking identifiable open reading frames (with rare exceptions). Herein, we highlight emerging evidence demonstrating that lncRNAs are critical regulators of liver metabolic function and diseases. We summarize current knowledges about dysregulated lncRNAs and outline the underlying molecular mechanisms by which lncRNAs control hepatic lipid ad glucose metabolism, as well as cholestatic liver disease. lncLSTR, Lnc18q22.2, SRA, HULC, MALAT1, lncLGR, MEG3, and H19, lncHR1, lnc-HC, APOA1-AS, DYNLRB2-2, and LeXis are included in the discussion.

Keywords

Long non-coding RNA; liver; lipid metabolism; glucose metabolism; cholestatic liver disease

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Conflict of interest

Nothing to disclose.

1. Introduction

With the development of high-throughput RNA sequencing technology in transcriptome analysis and bioinformatics prediction, RNA transcripts, that do not code proteins but that may have biological functions, have provided a new perspective in major physiological and pathological processes. It is estimated that more than 80% of the human genome is pervasively transcribed; however, protein-coding genes account for less than 2% of the human genome.[1] This leaves the balance of the human genome to be transcribed into thousands of non-coding RNAs (ncRNAs). According to size, the ncRNA transcripts are arbitrarily categorized into two main subgroups: short ncRNA (<200bp) and long ncRNAs (lncRNAs) (>200bp). Short ncRNAs include highly abundant and functionally important RNAs such as transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs), as well as small regulatory RNAs such as microRNAs, siRNAs, wipi-interacting RNA (piRNA).[2] While lncRNAs are commonly defined as transcripts of more than 200 nucleotides in length that are not capable of being translated into proteins.[3] Extensive studies have been conducted on miRNAs, however the functions of lncRNAs remain poorly understood.[4,5] Recent studies have revealed that lncRNAs significantly impact on various biological processes as X-inactivation, genomic imprinting, chromatin modification, cell fate specification, cell apoptosis, nuclear trafficking, and genome rearrangement.[6]

Herein, we focus on the role of lncRNAs in liver metabolic functions and associated liver diseases. This new emerging research field is expected to significantly increase our understanding the fundamental mechanisms contributing to various liver diseases with the goal of developing new diagnosis, prognosis and treatment strategies.

2. Characteristics of lncRNA

The majority of lncRNA are transcribed from RNA polymerase II and are often capped, spliced and poly-adenylated.[7] Unlike mRNAs, lncRNAs are poorly conserved between humans and rodents. lncRNAs are expressed in a species- and tissue-specific, and developmentally regulated manner which may contribute to their unique function.[8] Based on relationship to their location relative to that of nearby protein-coding genes, lncRNA are currently classed into five categories, namely i) sense; ii) antisense; iii) bidirectional; iv) intronic; and v) intergenic.[9] As gene expression regulators, lncRNAs are involved in chromatin remodeling, epigenetic regulation, transcriptional and post-transcriptional regulation, processing of small RNAs, protein function, and other regulatory processes.[10] Mechanistically, molecular functions of lncRNAs are described as signals, decoys, guides, and scaffolds.[11] The specific expression in specific cell types and stages of development as well as the response to environmental stimuli make lncRNAs as effective signals. As decoys, lncRNAs bind and promote protein degradation. LncRNAs can also bind and recruit regulatory molecules such as chromatin remodelers and transcription factors to specific gene targets to control gene expression. By binding different molecules with different domains, lncRNAs can also act as scaffolds, assembling a functional complex.[12]

3. LncRNAs in hepatic lipid and glucose metabolism

As the major site for synthesis, metabolism, storage, and redistribution of carbohydrates, proteins, and lipids, liver plays a central role in metabolic homeostasis.[13] Emerging studies have shown that many lncRNAs are key regulators of lipid and glucose metabolism. Lipid accumulation in liver is determined by the balance between lipogenesis and catabolic processes such as lipolysis, fatty acid b-oxidation and thermogenesis.[14] The maintenance of glucose homeostasis results from the balance of glucose production and/or storage in the liver and glucose uptake in the peripheral tissues.[15] Dysregulation of these processes leads to adiposity, dyslipidemia, and metabolic perturbations.[16]

3.1 lncLSTR

Analysis of metabolic organ-enriched lncRNA identified that lncLSTR exhibits liver-specific expression and its expression fluctuates in response to changes in energy levels and metabolic state.[17] LncLSTR is an intergenic lncRNA and liver-specific knockdown of lncLSTR significantly reduced plasma triglyceride (TG) via enhancing tissue TG clearance. This reduced circulating level of TG in lncLSTR knockdown mice resulted from increased apoC2 expression and LPL activities through a FXR-mediated pathway. Mechanistically, lncLSTR has been shown to directly bind to TDP43, further relieve the transcriptional suppression of Cyp8b1 and lead to substantial change in bile acid composition. The altered bile composition activate FXR and apoC2 expression, resulting in enhanced TG clearance in mice.

3.2 Lnc18q22.2

Lnc18q22.2, a liver-specific lncRNA (RP11-484N16.1) on chromosome 18, has been shown to be markedly induced in the liver tissue of NASH patients, correlating with NASH grade, lobular inflammation and NAS score.[18] Interesting, lnc18q22.2 is significantly associated with liver steatosis and steatohepatitis, but not with hepatocellular carcinoma in 44 independent liver biopsies. Knockdown of lnc18q22.2 in hepatocyte cell lines reduced cell viability and promoted necrosis.

3.3 SRA

A steroid receptor coactivator, SRA, was reported existing in an SRC-1 complex and functioned as an RNA coactivator for non-steroid nuclear receptors.[19] A recently study showed that the expression of liver adipose triglyceride lipase (ATGL) is induced in SRA knockout mice.[20] SRA suppresses ATGL via inhibiting transcriptional activity of FOXO1 in an insulin-independent pathway, thus reducing FFA β-oxidation and promoting hepatic steatosis. SRA is also the first lncRNA reported to play a potential role in adipogenesis through regulation of PPARγ and P38/JNK phosphorylation.[21]

3.4 HULC

Highly upregulated in liver cancer (HULC), the first identified lncRNA specifically overexpressed in hepatocellular carcinoma (HCC), has been shown as an effective prognostic biomarker in many human cancers.[22,23] HULC can be posttranscriptional destabilized by IGF2BP1 via recruiting the CCR4-NOT deadenylase complex, a major

component of the cytoplasmic RNA decay machinery.[24] A recently study showed that HULC induced methylation of CpG islands in the miR-9 promoter through upregulation of DNMT1.[25] The downregulation of miR-9 further enhanced lipogenesis and enriched intracellular triglycerides and cholesterol by activating PPARγ and ACSL1 in hepatoma cells.

3.5 MALAT1

Metastasis associated in lung adenocarcinoma transcript 1 (MALAT1) is involved in the development of HCC and liver fibrosis.[26,27] A recently study showed that MALAT1 promoted hepatic steatosis and insulin resistance. MALAT1 induced hepatic lipid accumulation and insulin resistance by interacting with SREBP-1c and stabilizing its protein in hepatocytes.[28] Knockdown of MALAT1 effectively reversed lipid aggregation and increased insulin sensitivity in ob/ob mice.

3.6 lncLGR

Glucose levels in mammals is tightly controlled through multiple mechanisms to meet systemic energy demands. As the major site of glucose regulation, the liver produces glucose through glycogenolysis and gluconeogenesis during fasting, while promoting glucose uptake and glycogen storage during feeding. Liver glucokinase repressor (lncLGR), a fasting-induced lncRNA in the liver, has been shown to suppress glucokinase (GCK) transcription and glycogen storage in fasted mice.[29] Mechanistically, lncLGR specifically binds to heterogenous nuclear ribonucleoprotein L (hnRNPL), an RNA-binding protein which is further confirmed to be recruited to the promoter of GCK and suppress its transcription.

3.7 MEG3

Maternally expressed gene 3 (MEG3) is upregulated in high-fat diet and ob/ob mice through histone acetylation.[30] Knockdown of MEG3 remarkably abolishes hepatic TG accumulation, up- regulates glycogen content, and promotes glucose tolerance in high-fat diet mice and ob/ob mice. Another study showed that MEG3 was highly expressed in mouse islets and was down- regulated during the pathogenesis of diabetes.[31] Moreover, the expression of MEG3 was modulated by glucose both *in vitro* and *in vivo*. Knockdown of MEG3 reduced insulin synthesis, secretion, and increased beta cell apoptosis, leading to impaired glucose tolerance.

3.8 H19

H19 is one of the first discovered lncRNAs highly expressed in fetal mouse and human liver, but repressed in adult liver by zinc fingers and homeoboxes 2 (Zhx2).[32] H19 is significantly up- regulated in mouse model of CCl4-induced tumors and in human fibrotic/cirrhotic liver.[33] H19 plays a role in affecting transcription through chromatin remodeling. One study related H19 to steatosis by a lipid droplet protein PLIN2 which was significantly induced in fatty liver.[22] H19 was up-regulated in the liver of high fat diet fed PLIN2 knockdown mice with decreased hepatic TG level.

3.9 lncHR1

LncHR1 was recently identified as a novel human specific lncRNA, which was shown to reduce hepatic and plasma TG levels along with decreased expression of SREBP1c, FAS, and ACCα in high-fat diet model. In Huh7 cells, lncHR1 abolished oleic acid induced TG accumulation and cytosolic lipid droplets. Mechanistically, lncHR1 regulates hepatic lipid metabolism by suppressing SREBP1c promoter activity and negatively regulating SREBP1c and FAS expression.[34]

4. LncRNA in cholestatic liver disease

In hepatocytes, cholesterol homeostasis is maintained by a complex network involving cholesterol uptake, synthesis, intracellular transport, and excretion.[35] As the end-products of cholesterol catabolism in the liver, bile acids (BAs) are secreted by the liver to aid in the digestion of fats and are reported as signaling molecules that regulate glucose, lipid, and energy metabolism.[13,36] Cholestasis is a pathological condition that BAs are blocked to flow out of liver, resulting intrahepatic accumulation. High levels of toxic BAs cause bile duct epithelium damage, hepatocytes injury and inflammation.[37] Chronic cholestasis then leads to liver fibrosis, cirrhosis, liver failure, hepatocellular arcinoma, and cholangiocarcinoma.

4.1 lnc-HC

A novel lncRNA named lnc-HC is up-regulated in HFD MetS rat liver to negatively regulate cholesterol metabolism by physically interacting with hnRNPA2B1 in hepatocytes.[38] The lnc-HC- hnRNPA2B1 complex further binds to two target message RNAs Cyp7a1 or Abca1; both are critical for the conversion of cholesterol into BAs and for facilitating cholesterol efflux. Knockdown of lnc-HC significantly recovers glucose tolerance disorder, and improves total cholesterol, TG, and HDL-cholesterol in the HCD rat model.

4.2 APOA1-AS

Another potential group of lncRNAs that consist of 70% of total lncRNAs is natural antisense transcripts (NATs), which regulate sense gene expression in a positive or negative manner. APOA1-AS is transcribed from the opposed DNA strand to APO gene cluster and negatively regulates APOA1 expression in vitro and in vivo. As the major protein component of high- density lipoprotein in plasma and cofactor for the lecithin cholesterol acyltransferase, APOA1 plays a significant role in reverse cholesterol transport, promoting cholesterol efflux from tissues.[39] APOA1-AS epigenetically inhibits APOA1 expression and multiple neighboring genes, though LSD1 and SUZ12 recruitment.[40]

4.3 H19

We reported that hepatic H19 expression was strikingly induced in Bcl2-induced cholestatic liver injury, which was alleviated by knockdown of H19.[41] Hepatic overexpression of H19RNA facilitated the development of obstructive cholestatic liver fibrosis.[42] Mechanistically, H19 downregulated hepatic zinc finger E-box-binding homeobox 1 (ZEB1), and impeded its suppression of epithelial cell adhesion molecule (EpCAM), which in turn augmented bile duct ligation (BDL)-induced liver fibrosis. In addition, H19RNA is upregulated in both PBC and PSC patients. Another group reported a similar role of H19 in

cholestasis. H19 was shown to be representing a key factor that causes the gender disparity of cholestatic liver injury not only in Mdr2 KO mice, and probably in human PSC patients.[4]

4.4 MEG3

MEG3, which was shown to promote hepatic insulin resistance, was down-regulated in the liver of mice fed with DDC.[30,43] Recently, MEG3 was identified as a guide RNA scaffold to recruit PTBP1 to destabilize nuclear receptor Shp mRNA in cholestatic liver injury.[44] Overexpression of MEG3 RNA induced a rapid Shp mRNA degradation and elevation of liver injury enzymes such as ALT and AST in mouse liver, and disrupted bile acids homeostasis. Moreover, the expression of MEG3 was also inhibited by SHP via a CREB-dependent feedback regulation.

4.5 DYNLRB2-2

lincRNA-DYNLRB2-2 was reported to be significantly induced in THP-1 macrophage-derived foam cells by Ox-LDL in a dose and time-dependent manner.[45] Up-regulated lincRNA- DYNLRB2-2 promoted ABCA1 expression, which plays an essential role in cholesterol metabolism and inflammation, via inducing the expression of G protein-coupled receptor 119 (GPR119) and activating GLP-1R pathway.

4.6 LeXis

Liver-expressed LXR-induced sequence (LeXis), an lncRNA robustly induced in primary mouse hepatocytes treated with LXR agonist GW3965, decreased serum cholesterol, but not triglycerides in a mouse model.[46] LeXis has been shown to inhibit cholesterol biosynthesis by associating with and affecting the DNA interaction of Raly which is required for the maximal expression of cholesterologenic genes in mouse liver.

5. Conclusions and future perspectives

LncRNAs control several important aspects of liver function involved in the pathophysiology of human liver injury and disease.[5] The microRNAs (miRNAs) comprise a class of short single- stranded non-coding RNAs that regulate gene expression mainly through post-transcriptional regulation by binding to the 3′UTRs of target mRNAs. For example, a new study demonstrated that miR-127 modulates the pluripotency of liver tumor initiating cells by targeting HMGB2.[47] Compared to miRNAs, lncRNAs can exert their diverse functions through interaction with proteins, miRNAs and mRNAs.[48] Hepatocellular carcinoma (HCC) is one of the most common cancers in the world.[49] Recent studies have also identified the critical roles of lncRNAs in the pathogenesis and metastasis of HCC through regulating tumor growth and proliferation, metastasis and invasion, and apoptosis.[48] Novel concepts related to lncRNAs and liver physiology have been successfully integrated into the drug development process to develop effective therapies. Continued efforts are still needed to expand the current knowledge in order to develop lncRNA-based therapeutics for the treatment of chronic liver diseases.

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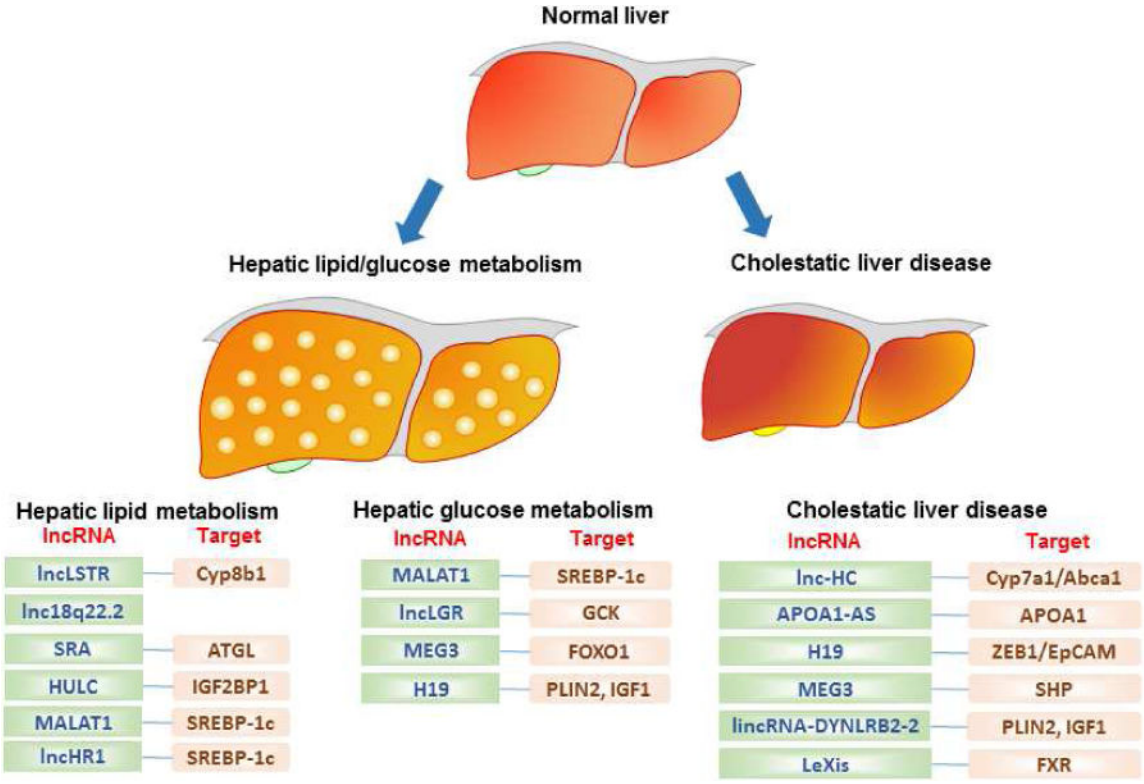

Figure 1.

Diagram depicting the regulatory role of lncRNAs in live metabolism and disease. LncRNAs (*dark blue*) are presented in three groups based on their function. Target genes are indicated on the right side of each lncRNAs (*brown*).

Table 1

LncRNAs in Metabolic Liver Diseases

Metabolic liver diseases	LncRNAs	Reference
Hepatic lipid metabolism	lncLSTR	[17]
	Lnc18q22.2	[18]
	SRA	[19],[20],[21]
	HULC	[24],[25]
	MALAT1	[28]
	LncHR1	[34]
Hepatic glucose metabolism	MALAT1	[28]
	lncLGR	[29]
	MEG3	[30],[31]
	H19	[22],[32]
Cholestatic liver disease	lnc-HC	[38]
	APOA1-AS	[39],[40]
	H19	[4],[41],[42]
	MEG3	[30],[43],[44]
	lincRNA-DYNLRB2-2	[45]
	LeXis	[46]